Genome-wide association study identifies nox3 as a critical gene for susceptibility to noise-induced hearing loss.

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Public Summary:
Genome-wide association studies in humans have been successful in identifying new genes that are associated with complex traits, but some studies, depending on the trait of interest, are limited by the ability to collect accurate data in large numbers of people. For instance, noise-induced hearing loss (NIHL) is the most common work-related disease in the world, and the second cause of hearing loss. Despite the impact of this syndrome on the human population, it has been difficult to pinpoint underlying causal genetic effects, because the impact of the environment on NIHL is highly variable in humans and is unlikely to be accurately measured for every individual in a large-scale study. By performing a genome-wide analysis in mice, however, the environment can be carefully controlled, facilitating the study of complex traits like NIHL. In this manuscript, we successfully identify Nox3 as an associated gene for susceptibility to NIHL, demonstrating the advantages of performing GWAS in a mouse model for traits that are difficult to study in humans.

Scientific Abstract:
In the United States, roughly 10% of the population is exposed daily to hazardous levels of noise in the workplace. Twin studies estimate heritability for noise-induced hearing loss (NIHL) of approximately 36%, and strain specific variation in sensitivity has been demonstrated in mice. Based upon the difficulties inherent to the study of NIHL in humans, we have turned to the study of this complex trait in mice. We exposed 5 week-old mice from the Hybrid Mouse Diversity Panel (HMDP) to a 10 kHz octave band noise at 108 dB for 2 hours and assessed the permanent threshold shift 2 weeks post exposure using frequency specific stimuli. These data were then used in a genome-wide association study (GWAS) using the Efficient Mixed Model Analysis (EMMA) to control for population structure. In this manuscript we describe our GWAS, with an emphasis on a significant peak for susceptibility to NIHL on chromosome 17 within a haplotype block containing NADPH oxidase-3 (Nox3). Our peak was detected after an 8 kHz tone burst stimulus. Nox3 mutants and heterozygotes were then tested to validate our GWAS. The mutants and heterozygotes demonstrated a greater susceptibility to NIHL specifically at 8 kHz both on measures of distortion product otoacoustic emissions (DPOAE) and on auditory brainstem response (ABR). We demonstrate that this sensitivity resides within the synaptic ribbons of the cochlea in the mutant animals specifically at 8 kHz. Our work is the first GWAS for NIHL in mice and elucidates the power of our approach to identify tonotopic genetic susceptibility to NIHL.